SCIENCE

VOL. 82 FRIDAY, AUGUST 23, 1935 No. 2121

The Etiology of Pernicious and Related Macrocytic Anemias: DR. WILLIAM B. CASTLE 159

Scientific Events:

Courses in Game Management at the State Universities; The Leverhulme Fellowships and Awards for Research; The Oxford Congress on Soil Science; Meeting of Mathematicians at Ann Arbor. Recent Deaths 164

Scientific Notes and News 167

Discussion:

Minnesota Man—A Discussion of the Site: PROFESSOR KIRK BRYAN. *The Occurrence of Anopheles maculipennis in Mexico:* DR. ALF. DAMPF. *Eggs of a Peneid Shrimp:* JOHN C. PEARSON. *An Anomalous Muscle in the California River Otter:* EDNA M. FISHER. *The Effect of Prolactin on the Estrus Cycle of Non-parous Mice:* IRMGARD DRESEL 170

Scientific Books:

Faraday: PROFESSOR W. F. MAGIE. *Applied Entomology:* DR. L. O. HOWARD 173

Special Articles:

X-Ray Reflections of Long Spacing from Tendon: DR. RALPH W. G. WYCKOFF, DR. ROBERT B. COREY and J. BISCOE. *Oral Immunization to Colds:* DR. GEORGE E. ROCKWELL, HERMANN C. VAN KIRK and DR. H. M. POWELL. *A "Growth Substance":* PROFESSOR ROGER J. WILLIAMS and BERT E. CHRISTENSEN 175

Scientific Apparatus and Laboratory Methods:

A Method of Preparing Paraffin Sections of Bone: DR. LORNA THIGPEN DAVID. *Apparatus for Heavy Water Studies in Small Animals:* DR. HENRY G. BARBOUR and F. J. COCHRAN 179

Science News 6

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. MCKEEN CATTELL and published every Friday by

THE SCIENCE PRESS

New York City: Grand Central Terminal

Lancaster, Pa. Garrison, N. Y.

Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

THE ETIOLOGY OF PERNICIOUS AND RELATED MACROCYTIC ANEMIAS*

By Dr. WILLIAM B. CASTLE

BOSTON, MASS.

THE student of dietary deficiency disorders is usually concerned with the relationship of defects in the composition of the diet to such diseases. There is, however, evidence that nutritional disturbances may be complicated or actually induced by the presence of sufficient pathological changes in the alimentary tract to interfere with the digestion or assimilation of food adequate for the normal individual. As a result of observations carried out during the past eight years, it is our belief that Addisonian pernicious anemia and certain related macrocytic anemias present examples of such a process and afford an opportunity for the study of a somewhat specialized mechanism which is apparently responsible for the prevention of such anemias in the normal individual. The concept of these anemias as in many instances manifestations of "conditioned" deficiency disease has been developed through studies made in association at various times with Dr. Wilmot C. Townsend, Dr. Clark W. Heath, Dr. Maurice B. Strauss, Dr. Herman A. Lawson and Dr. C. P. Rhoads. Dr. Strauss has been especially concerned with the problems of the macrocytic anemia of pregnancy; and Dr. Rhoads has since made notable contributions to the understanding of the macrocytic anemias, especially of sprue. If the results of the observations, which are summarized below, seem lacking in detail, it is largely because studies carried out in man must be made as opportunity is afforded by the clinical material. On the other hand, in animal experiments there is

* Read before the Harvey Society on October 18, 1934. From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard University Medical School, Boston, Mass.

always a possibility that the results may not be directly applicable to the human species.

When this work was begun in 1927, three pertinent facts had been established concerning pernicious anemia. The absence of free hydrochloric acid in the gastric secretion had been shown to be an almost constant finding. The megaloblastic hypertrophy of the bone marrow had been shown by Peabody[1] to be the result of arrested development of the red blood cells with consequent diminished blood production. Minot and Murphy[2] had shown that the administration of liver regularly and promptly caused pronounced improvement of the blood and of the clinical condition of the patients. This fact especially made it a logical conclusion that pernicious anemia was a disease due either to a metabolic defect or in some sense to dietary deficiency.

The etiological significance of the defective gastric secretion had been suggested in 1880 by Fenwick,[3] whose surmise in this respect can scarcely be bettered to-day. He believed that, as a result of the gastric atrophy which he observed post-mortem, defective digestion of the "albuminous material" of the food led to a condition in which "the various tissues were starved of their usual supply of nourishment." Faber[4] and Hurst[5] are especially responsible for the continued interest in the causative rôle of achlorhydria. Hurst believed that it allowed the development of an abnormal type of bacterial flora in the intestinal canal. To us it appeared that the "deficiency" hypothesis of Fenwick was more consistent than the "bacterial" hypothesis with the then recently discovered facts concerning the results of therapy with liver. Because of the possibility of easily observing effects upon blood formation, especially by means of the reticulocyte reaction already employed by Minot and his associates,[6] the problem was attacked directly. It was postulated that "the significant defect in the patient with pernicious anemia is an inability to carry out some essential step in the process of gastric digestion thus causing a lack of whatever substance is successfully derived by the stomach of the normal individual from his food."

The technique of the observations consisted in the daily administration to suitable patients with Addisonian pernicious anemia of various preparations of normal human gastric juice and beef muscle alone or in combination. A preliminary incubation, entirely unnecessary for the production of the effects observed, rendered the material sufficiently liquid to pass through a small stomach tube. To provide a control inherent in each patient, so far as was possible a first period of ten to fourteen days of the administration of a substance without activity was followed by a second period of similar length during which an effective substance was given. In order to exclude other sources of hematopoietic material than those specifically administered, the patients were maintained on diets containing no meat, liver or kidneys and very little egg, poultry or fish. The incubated mixtures were given to the patients at least six hours after any food had been taken. The results of these observations have been published elsewhere in full[7, 8, 9, 10, 11] and will be only briefly summarized here.

The daily administration of 200 grams of beef muscle as such or after digestion with pepsin and hydrochloric acid was without significant effect. The daily administration of 300 cc of human gastric juice secreted by normal fasting subjects in response to the injection of histamine was likewise ineffective. When normal human gastric juice and beef muscle were given together, however, with or without preliminary incubation at pH 2.5 to 3.5 and subsequent adjustment to pH 5 to 7, reticulocyte responses, increases of the red blood cells and hemoglobin and clinical improvement promptly appeared and continued so long as the material was administered, quite as if moderate amounts of liver were being given. It was therefore evident that the increased blood formation depended upon the interaction of two factors, one in the beef muscle (extrinsic) and one in the normal human gastric juice (intrinsic). It was also clear that in the patient with pernicious anemia the gastric factor was lacking. Attempts were then made to learn something of the properties of these factors and the site and conditions of their interaction.

The gastric factor has not been identified with any known constituent of the normal gastric secretion. It has been shown not to be hydrochloric acid, pepsin, rennin or lipase. It is present in the gastric secretions of certain patients with gastric achlorhydria who either have no anemia or have other types of

[1] F. W. Peabody, *Am. Jour. Path.*, 3: 179–202, 1927.
[2] G. R. Minot and W. P. Murphy, *Jour. Am. Med. Assn.*, 87: 470–476, 1926.
[3] S. Fenwick, "On Atrophy of the Stomach and on the Nervous Affections of the Digestive Organs," J. and A. Churchill, London, 1880.
[4] K. Faber, *Berlin. klin. Wchnschr.*, 1: 958–962, 1913.
[5] A. F. Hurst, *Lancet*, 1: 111–115, 1923.
[6] G. R. Minot, W. P. Murphy and R. P. Stetson, *Am. Jour. Med. Sci.*, 175: 581–599, 1928.
[7] W. B. Castle and E. A. Locke, *Jour. Clin. Invest.*, 6: 2–3, 1928.
[8] W. B. Castle, *Am. Jour. Med. Sci.*, 178: 748–764, 1929.
[9] W. B. Castle and W. C. Townsend, *Am. Jour. Med. Sci.*, 178: 764–777, 1929.
[10] W. B. Castle, W. C. Townsend and C. W. Heath, *Am. Jour. Med. Sci.*, 180: 305–335, 1930.
[11] W. B. Castle, C. W. Heath and M. B. Strauss, *Am. Jour. Med. Sci.*, 182: 741–764, 1931.

anemia than pernicious anemia. It may be absent from the gastric secretion in certain cases of pernicious anemia in the presence of normal amounts of hydrochloric acid and pepsin. The intrinsic factor is not present in normal human saliva or duodenal contents from which gastric juice has been excluded. It is readily destroyed by heat: boiling for five minutes, heating to 70° to 80°C. for half an hour, or to 40°C. for three days.

The food factor has also not been identified. It is present in beef muscle, eggs,[12, 13] autolyzed yeast, rice polishings and wheat germ.[14] Reimann has demonstrated it in liver;[15] and Fouts, Helmer and Zerfas[16] have found it in the liver fraction "G" of Cohn, Minot and their associates.[17] Hydrolysis of this liver extract with dilute sulphuric acid until its active principle for pernicious anemia has been destroyed, does not destroy the extrinsic factor. The substance in autolyzed yeast is capable of resisting autoclaving for five hours at 15 pounds pressure and is soluble in 80 per cent. alcohol. It is not present in leached casein, wheat gluten or in animal or yeast nucleic acid. Because of these properties we[18] suggested in 1932 that the extrinsic factor might be vitamin B_2, employing the term as synonymous with vitamin G. Since then others[19, 20, 21] have been unable to identify it with any portion of the vitamin B complex as defined by growth experiments in animals. Because whole yeast and aqueous extracts of yeast could not be shown to contain extrinsic factor, Wills[19] has suggested that the process of autolysis of yeast is responsible for the production of extrinsic factor.

The precise conditions necessary for the interaction of the food and gastric factors can scarcely be defined, since the site of their interaction is unknown. We have found that no effect takes place unless these substances are administered to the patient at approximately the same time. If a mixture incubated at pH 2.5 to 3.5 is not brought to pH 5 to 7 before administration, then also no effect is observed. These facts suggest, but do not prove, that at least one stage in the process of the formation of the end product active upon the bone marrow takes place in the gastrointestinal tract presumably at or near neutrality. We have attempted to discover the locus of this reaction by determining whether a thermostable product similar to the active principle of liver was formed *in vitro*. Appropriate incubations of beef muscle with normal human gastric juice and also subsequently with normal human duodenal contents at pH 7 do not lead to the production of a thermostable substance similar to that found in liver. Heating to 70° to 80°C. for half an hour or boiling for five minutes invariably destroys the activity of such preparations. Klein and Wilkinson's[22] claim to have synthesized the active principle of liver *in vitro* is not established by their experiments with beef muscle and hog stomach extracts, in which a temperature of only 60° to 70°C. for half an hour was found not to destroy the activity. In order to establish a thermal identity with the active principle of liver it is at least necessary to show that boiling is without destructive effect. It is, however, possible that Klein and Wilkinson have synthesized a precursor of the active principle of liver.

We have approached the problem of the site of interaction of the food and gastric factors by attempting to ascertain whether the parenteral injection of suitable mixtures of each after appropriate incubation leads to increased blood production in pernicious anemia. The results so far obtained have been so variable as not to enable us to answer this question. The chief obstacle is that the parenteral administration of materials containing protein or protein derivatives, though causing reticulocyte responses, is not necessarily associated with consistent increases of red blood cells or clinical improvement. For this reason certain evidence in the literature that the parenteral administration of gastric juice,[23] of preparations of hog stomach[24] and of digests of beef muscle and hog stomach[22] leads to specific effects comparable to those observed with oral administration must be accepted with caution. Fouts, Helmer and Zerfas[16] have shown that the reticulocytogenic substance in concentrated gastric juice[23] is not present until the material has been subjected to incubation. Wilkinson has shown that very large amounts of normal human gastric juice administered by mouth are ineffective in pernicious anemia. Experiments with orally administered substances do not support the idea that intrinsic factor is effective without inter-

[12] K. Singer, *Wien. klin. Wchnschr.*, 45: 1063, 1064, 1932.

[13] D. K. Miller and C. P. Rhoads, *New Eng. Jour. Med.*, 211: 921–924, 1934.

[14] W. B. Castle, *Ann. Int. Med.*, 7: 1–5, 1933.

[15] F. Reimann, *Med. Klin.*, 27: 880–881, 1931.

[16] P. J. Fouts, O. M. Helmer and L. G. Zerfas, *Am. Jour. Med. Sci.*, 187: 36–50, 1934.

[17] E. J. Cohn, G. R. Minot, G. A. Alles and W. T. Salter, *Jour. Biol. Chem.*, 77: 325–358, 1928.

[18] M. B. Strauss and W. B. Castle, *New Eng. Jour. Med.*, 207: 55–59, 1932.

[19] L. Wills, *Lancet*, 1: 1283–1286, 1933.

[20] H. C. A. Lassen and H. K. Lassen, *Am. Jour. Med. Sci.*, 188: 461–472, 1934.

[21] F. Diehl and J. Kühnau, *Deutsch. Arch. f. klin. Med.*, 176: 149–153, 1933.

[22] L. Klein and J. F. Wilkinson, *Biochem. Jour.*, 28: 1684–1692, 1934.

[23] R. S. Morris, L. Schiff, J. H. Foulger, M. L. Rich and J. E. Sherman, *Jour. Am. Med. Assn.*, 100: 171–173, 1933.

[24] W. Ederle, H. Kriech and M. Gänsslen, *Klin. Wchnschr.*, 10: 313, 1931.

action with extrinsic factor, although they do not exclude the possibility that this reaction may take place parenterally.

As a result of these observations, it is believed that a physiological mechanism exists in the normal individual which is usually absent in the patient with Addisonian pernicious anemia in relapse. Both the food and the stomach are involved in this process, which will obviously be initiated in the normal individual whenever extrinsic factor is taken in the food. It is logical to conclude that the integrity of this mechanism prevents the development of pernicious anemia in the normal individual; and that its absence leads to a deficiency of the active principle of liver and so to pernicious anemia. It is, however, evident that a deficiency of the active principle finally effective in the body might be brought about by at least three different types of derangement of this mechanism in the gastrointestinal tract.[11] A lack of intrinsic factor in the stomach, a lack of extrinsic factor in the food or a failure of the absorption or the destruction of these substances or their end product in the intestinal tract would have the same result. It is, moreover, possible for the participation of each of these derangements to be variable in different patients and at different times in the same individual. Furthermore, an interruption or inhibition within the body of any link in the chain of chemical events leading to the production of the end product active in the bone marrow would also have a similar effect. For the last supposition there is no detailed evidence at present except the variations in the effect of the parenteral administration of a given amount of the same liver extract in different patients with pernicious anemia; and the fact that arteriosclerosis and infections appear to be common in patients responding poorly to parenterally administered liver extract. The evidence that disease of the liver may specifically produce an interruption in the metabolism of the active principle of liver has not been convincingly established. The arguments in favor of such a supposition neglect the fact that the animal kidney is as effective a source of the active principle of liver as is that organ itself. Although much has been learned concerning the nature of the active substance in liver, especially through the work of Cohn[25] and West[26] and their respective associates, its precise nature remains unknown.

Deficiency of the gastric factor is apparently the dominant mechanism in Addisonian pernicious anemia in relapse. It is probable, however, that the gastric defect is relative rather than absolute. We[11] have demonstrated the recrudescence of gastric factor in one patient after treatment with liver extract. Such was also apparently the case in the patients observed by Barnett.[27] This observation probably explains the response of occasional patients with pernicious anemia to the oral administration of extrinsic factor, especially of autolyzed yeast in large amounts. Ungley and James[28] have recently shown that in such patients autolyzed yeast preparations are not effective when administered parenterally.

Sprue with macrocytic anemia, on the other hand, has been successfully treated by Elders,[29] Ashford[30] and others in some instances with diets rich in animal protein, and recently autolyzed yeast[31] has been found to be effective in some patients. Wills[32] has observed excellent results in the treatment of the macrocytic anemia of pregnancy in India with autolyzed yeast; and Vaughan and Hunter[33] have demonstrated reticulocyte responses and improvement of the blood values in the macrocytic anemia of idiopathic steatorrhea following the administration of autolyzed yeast. The fact that hydrochloric acid is often present in the gastric contents of such patients suggests that intrinsic factor was also present in sufficient amounts to interact with these sources of extrinsic factor. Although in certain cases of sprue intrinsic factor has been shown to be lacking,[31] the prevalence of defective diets in both sprue and the macrocytic anemia of pregnancy in India suggests that extrinsic factor defect is etiologically important.

In any of these types of macrocytic anemia defects of absorption apparently may be present and contribute to a deficiency of the active end product. In certain cases of pernicious anemia[11] and especially in advanced cases of sprue[31, 34] very large doses of liver extract are not effective when given by mouth. The fact that usual doses of parenterally administered liver extract are sometimes found to be normally effective suggests, but does not necessarily prove, that the orally administered material is not being adequately absorbed, because it is also known that the responses of different patients with pernicious anemia to the parenteral administration of the same amount of active principle vary considerably. Until it is known what are exactly comparable doses of a single

[25] E. J. Cohn, T. L. McMeekin and G. R. Minot, *Tr. Assn. Am. Phys.*, 45: 343–349, 1930.

[26] H. D. Dakin and R. West, *Jour. Biol. Chem.*, 109: 489–522, 1935.

[27] C. W. Barnett, *Am. Jour. Med. Sci.*, 182: 170–177, 1931.

[28] C. C. Ungley and G. V. James, *Quart. Jour. Med.*, 27: 523–548, 1934.

[29] C. Elders, *Lancet*, 1: 75–77, 1925.

[30] B. K. Ashford, *Ann. Clin. Med.*, 4: 13–20, 1925.

[31] W. B. Castle and C. P. Rhoads, *Lancet*, 1: 1198–1199, 1932.

[32] L. Wills, *Brit. Med. Jour.*, 1: 1059–1064, 1931.

[33] J. M. Vaughan and D. Hunter, *Lancet*, 1: 829–834, 1932.

[34] C. P. Rhoads and D. K. Miller, *Jour. Am. Med. Assn.*, 103: 387–391, 1934.

source of liver extract which can be given both orally and parenterally, it is impossible to come to a final conclusion. The clinical association of pernicious anemia with intestinal short circuits and stenoses and the morphological changes sometimes observed in the intestinal wall make the supposition of intestinal impermeability very likely. In the usual case of pernicious anemia the effectiveness of parenterally administered material appears to be at least sixty times as great as when given by the oral route. Whether this is entirely a physiological difference or whether it represents pathological changes in intestinal absorption is at present unknown.

It can also be demonstrated that the same participation of factors for the production of macrocytic anemia may not exist in a given patient at all times.[14] The fact that before the introduction of liver therapy it was often possible in the early stages of the disease to produce temporary remissions in patients with pernicious anemia by the use of high caloric diets rich in meat suggests that some intrinsic factor was still present. This is apparently much more frequently the case in early cases of sprue. The recrudescence of intrinsic factor has been demonstrated in a patient with pernicious anemia who originally secreted free hydrochloric acid without intrinsic factor in the gastric juice.[11] In the pernicious anemia of pregnancy, at least in some instances, the administration of extrinsic factor before delivery may produce no effect upon blood formation. After delivery, however, this material may induce clinical improvement and a reticulocyte response, which may then be augmented when normal gastric juice is added.[35] The disappearance of the intrinsic factor of the gastric juice during pregnancy is occasionally paralleled by the disappearance of the hydrochloric acid, which likewise may return after the birth of the child.

Objection may be raised to the hypothesis which we have developed on the basis that *total* extirpation of the stomach in man is not necessarily followed by the development of pernicious anemia even after several years. There are several reasons which render this criticism not necessarily valid. In the first place, the store of active principle in the liver, kidneys and other organs may be sufficient to prevent the anemia for some time. The parenteral injection at appropriate intervals of material derived from an amount of animal liver equivalent to the weight of that organ in man will suffice to maintain a patient with pernicious anemia in health for at least a year. Moreover, with surgical ablation of the stomach intestinal permeability is not necessarily affected, as is probable in the spontaneously developing disease. Since the liver, kidney and brain of normal animals have been shown to contain the active principle, it is possible that animal tissues more commonly consumed than these also contain smaller amounts of the same substance which might be readily absorbed from the normal intestine. Another explanation is provided by the studies of Meulengracht,[36] who has recently produced evidence that the active principle of hog stomach, the therapeutic value of which was first demonstrated by Sturgis and Isaacs,[37] is present largely in the pyloric region, where glands of a type closely resembling those of the duodenum of both man and the hog are found. Meulengracht has also shown that at least the upper portion of the hog's duodenum, like the pyloric region of the stomach, can be successfully used in the treatment of pernicious anemia. This observation suggests that surgical ablation of the entire stomach would still leave a source of intrinsic factor in the duodenum.

In 1921 McCarrison[38] published the results of experiments on deficiency disease in animals, which in the light of our observations appear to be even more significant than at the time of their publication. Whatever the difficulty of ascertaining the exact nature of the dietary defects or the influence of secondary infection in these experiments, it is clear that McCarrison was able to produce profound and wide-spread pathological changes in the alimentary tract. He noted degenerative changes in the secretory cells of the stomach and intestines and inferred that dietary deficiency causing alteration of the alimentary tract might result in secondary defects of nutrition. It is our belief that, when fully developed, Addisonian pernicious anemia is a deficiency disease conditioned, not so much by defective diet as by defects in the gastrointestinal tract. McCarrison's experiments, however, suggest a possible explanation for the original changes in the alimentary tract.

Recent observations by Miller and Rhoads[39] also tend to indicate the importance of McCarrison's observations, at least in respect to types of macrocytic anemia occurring in regions where defective nutrition is common. By the use of diets presumably defective in vitamin B_2 (G) or some closely related substance, these authors have been able to produce in swine a chronic condition analogous to black tongue in the dog studied by Goldberger and his associates. Their animals developed in many instances stomatitis,

[35] M. B. Strauss and W. B. Castle, *Am. Jour. Med. Sci.*, 185: 539–551, 1933.

[36] E. Meulengracht, *Acta med. Scandinav.*, 85: 79–88, 1935; *Proc. Roy. Soc. Med.*, 28: 841–870, 1935.

[37] C. C. Sturgis and R. Isaacs, *Jour. Am. Med. Assn.*, 93: 747–749, 1929.

[38] R. McCarrison, "Studies in Deficiency Disease," Henry Frowde and Hodder and Stoughton, London, 1921.

[39] D. K. Miller and C. P. Rhoads, *Jour. Clin. Invest.*, 14: 153–172, 1935.

gastric anacidity and macrocytic anemia responding to the administration of extracts of liver known to be effective in pernicious anemia. Of greatest immediate importance, however, is their observation that the intrinsic factor disappeared from the gastric juice of certain affected animals and that their livers were shown no longer to contain the thermostable principle effective in pernicious anemia. Here, then, is evidence that by a type of dietary deficiency the essential gastric defect of pernicious anemia has been produced. Although it is probable that defective diets are not the sole cause of such changes in Addisonian pernicious anemia, defective diets are very common in related types of macrocytic anemia such as occur in sprue and in pregnancy in certain parts of India. The facts disclosed by Miller and Rhoads must nevertheless be taken into account in any consideration of the possible original causes of the changes of the gastric secretion in Addisonian pernicious anemia. Even in this disease, aversion to meat was described by Fenwick[3] in 1880 and other peculiarities of the diet are often noted. Lindgren[40] has recently found that gastric anacidity in the general population is unusually common in Sweden in regions in which diets low in meat, vegetables and fruit and high in starchy foods are prevalent. It is hoped that students of nutritional deficiency may recognize that for an adequate explanation of the manifestations of deficiency disease in man the effects of dietary deficiency upon the gastrointestinal tract are worthy of further study.

SCIENTIFIC EVENTS

COURSES IN GAME MANAGEMENT AT THE STATE UNIVERSITIES

COURSES in game management, to be set up in the several state universities, will have the active support of the Bureau of Biological Survey, which is prepared to supply instructors and to cooperate with the universities and with state game commissions in financing the new development.

J. N. Darling, chief of the bureau, in announcing this new policy, stated that one of the leading American manufacturers of arms and ammunition has agreed to contribute $30,000 a year for the purpose. The Biological Survey will be able to supply $42,000. The game commissions and universities also will share in the expense.

Research work in wild-life subjects as well as in teaching the application of methods of modern game management will be included in the courses. Many universities now have important schools of forestry and it is anticipated that the new educational service in game management will follow similar lines.

Several schools and state game commissions are ready to proceed with the inauguration of courses in game management. The Biological Survey has men competent to direct the work. The courses will be designed to fit students with practical and scientific knowledge in game management and to turn out graduates equipped to do work in the restoration of valuable forms of wild life.

Mr. Darling points out that for years colleges and universities have been training foresters and park-planning engineers and developing specialists in the use and preservation of many of our natural resources, but nowhere are there facilities to prepare young men for the equally important task of administering the supply of wild birds, animals and fishes. As a result of this neglect there are few men who have the scientific and technical qualifications necessary to enable them to deal with the steady decrease in our wild life by applying the known principles of game restoration.

Under this new policy the Biological Survey will supply institutions with technically trained instructors who will make available to students, farmers, landowners and sportsmen the results of experimental work conducted by the wild-life agencies of state and federal governments and by conservation organizations. These units under the direction of the Bureau of Biological Survey will do away with this duplication of effort.

THE LEVERHULME FELLOWSHIPS AND AWARDS FOR RESEARCH

AWARDS of Leverhulme Research Fellowships in 1935 and grants to research workers are announced by the Advisory Committee and are given below. The Advisory Committee have recommended and the trustees have approved 20 nominations to fellowships and seven grants in aid of research, tenable for varying periods up to two years.

The names of the fellows and the subjects of the researches in the sciences are as follows:

W. N. BAILEY, M.A., D.Sc., senior lecturer in mathematics, University of Manchester.—"The Study of Functions of Hypergeometric Type."

D. B. BLACKLOCK, M.D., D.P.H., professor of tropical Medicine, University of Liverpool.—"A Study of the Present Practise of Hygiene (including Rural Hygiene) in Certain Eastern Countries."

MRS. M. G. BLACKLOCK, B.Sc., M.B., B.Ch., curator of the museum, Liverpool School of Tropical Medicine.—"A Comparative Study of the Organizations for the Improvement of Health of Women and Children in Eastern Countries."

[40] S. Lindgren, *Acta med. Scandinav.*, Suppl. 48: 1–235, 1932.

C. DARYLL FORDE, B.A., Ph.D., professor of geography and anthropology, University of Wales, Aberystwyth.—"Field Study of the Economy of a West African Village Community."

S. D. GARRETT, B.A., formerly assistant plant pathologist, Waite Agricultural Research Institute, University of Adelaide, South Australia.—"The Biological Antagonism of the Soil Microflora towards Root Disease Fungi of Crop Plants."

MRS. K. LONSDALE, D.Sc., research worker, Royal Institution, London.—"Relation between Structure and Physical Properties of Organic Molecules."

E. P. MUMFORD, M.A., M.S.C., late director, Pacific Entomological Survey, Honolulu.—"Terrestrial and Freshwater Biota of the Marquesas Islands."

R. G. W. NORRISH, B.A., Ph.D., director of studies, Emmanuel College, Cambridge.—"The Mechanism of Certain Chemical Reactions."

F. R. PERRY, M.Sc., member of research department, Metropolitan-Vickers Electrical Company, Limited, Manchester.—"The Study of Over-voltages Due to Lightning on Transmission Lines."

L. R. WAGER, M.A., B.Sc., lecturer in mineralogy and petrology, University of Reading.—"The Tertiary Igneous History of East Greenland."

W. D. WARE, washery supervisor, Cefn Coed Colliery, Crynant, South Wales.—"Research on the Lower Part of the Coal Measures and Millstone Grit in Pembrokeshire."

Grants in aid of research have been made to the following:

P. FORD, B.Sc., Ph.D., head of department of economics, University College, Southampton.—"Statistical Inquiries into Sources of Family Income."

R. D'OYLEY GOOD, M.A., head of department of botany, University College, Hull.—"A Botanical Survey of Dorset."

J. W. HESLOP HARRISON, D.Sc., F.R.S., professor of botany, Armstrong College, Newcastle.—"Genetical and Evolutionary Studies with Special Reference to Closely Allied Species and Local Races."

J. W. LAYARD, B.A.—"The Social Anthropology of North-Eastern Malekula and Allied Cultures."

J. W. W. STEPHENS, M.D., D.P.H., emeritus professor of tropical medicine, University of Liverpool.—"Treatise on Blackwater Fever in Its Historical, Clinical and Other Aspects."

THE OXFORD CONGRESS ON SOIL SCIENCE

OVER 400 workers in the particular branch of agricultural research which is known as soil science, or pedology, opened the third International Congress at Oxford on July 30. The congress continued until August 7, and afterwards, according to the London *Times*, 200 of the delegates toured Britain, in the course of which three days, from August 11 to 14, were spent in Aberdeen. The *Times*, writing in advance of the meeting, says:

> The chief object of their visit to Aberdeen is to inspect the Macaulay Institute for Soil Research at Craigiebuckler. There are only two centers in the British Isles which are devoted to scientific research on soils, one being the Rothamsted Experimental Station at Harpenden and the other the Scottish Station at Craigiebuckler. This, the most recent addition to Aberdeen's scientific institutions, was founded in 1930, when Mr. T. B. Macaulay, the president of the Sun Life Assurance Company of Canada, purchased the property of Craigiebuckler and provided a sum of money which made possible the establishment of a Scottish soil research institute. He was also responsible for the provision of a fully equipped demonstration farm on the Island of Lewis, which forms part of the institute. During the past five years the Macaulay Institute, the director of which is Dr. W. G. Ogg, has carried out much valuable work.
>
> Previous soil congresses were held in the United States in 1927 and in Russia in 1930. Many notable figures in the world of science will attend the Oxford congress. The president of the International Society of Soil Science, under whose auspices the congress is held, is Sir John Russell, the director of the Rothamsted Experimental Station, which is the oldest agricultural research station in the world. The secretary of the society is Dr. D. J. Hissinck, the director of the Soil Science Institute at Groningen, in Holland. Dr. Hissinck took a prominent part in the reclamation of the Zuider Zee, one of the most interesting agricultural achievements of modern times. Dr. Marbut, who has been responsible for the preparation of a soil map of the United States, and Dr. Stremme, of Danzig, who has prepared the first soil map of Europe, will be at the congress, and it is hoped they will take part in the post-congress tour.
>
> About 30 countries will be represented in the post-congress tour. The United States has sent the largest contingent of members to the congress; there are a few Canadian workers, and Russia and Germany are well represented. India has sent seven representatives, and Africa about the same number. China, Denmark, Norway, Sweden, Japan, Egypt, Palestine, Estonia, Finland, Czechoslovakia, Holland, Hungary, Rumania, Poland and France are all represented. Hawaii and the West Indies have also sent members.

The delegates were welcomed by the vice-chancellor of the university at the opening session, and were entertained by the Government at a dinner in Christ Church Hall on July 31. The meetings were arranged so that questions of wide interest were discussed in the mornings at plenary sessions, and more specialized ones in the afternoons at commission sessions. The presidential address of Sir John Russell was on "The Place of Soil Science in Agriculture," and Professor G. W. Robinson presented a general survey of British soils. There was a plenary session of Commission IV—Soil Fertility.

MEETING OF MATHEMATICIANS AT ANN ARBOR

THE annual summer meeting of mathematicians will take place at Ann Arbor from September 9 to 13. At this time there will be sessions of the American Mathematical Society, the Mathematical Association of America and the newly formed Institute of Statisticians.

The meetings of the association will occur on Monday afternoon and Tuesday morning and evening. At this time papers on the following topics will be given:

"The Confusion in Secondary Mathematics and Its Influence in the Teaching of Mathematics," by Professor K. P. Williams, Indiana University.

"Geometric Constructions without the Classical Restriction to Ruler and Compasses," by Professor W. H. Bussey, University of Minnesota.

"On an Introduction to Higher Geometry," by Professor Tibor Radó, the Ohio State University.

"Some Recent Applications of the Theory of Elasticity," by Professor H. W. March, University of Wisconsin.

"Operational Calculus, Its Applications and Foundations," by Dr. Hillel Poritsky, The General Electric Company.

"Some Unsolved Problems of Topology," by Professor R. L. Wilder, University of Michigan.

"Early Mathematical Books in the Library of the University of Michigan," by Professor L. C. Karpinski, University of Michigan.

The program of the society, extending from Tuesday afternoon to Friday afternoon, will consist of a series of colloquium lectures, two invited addresses and an unusually large number of short contributed papers.

The colloquium lectures will be delivered by Professor H. S. Vandiver, of the University of Texas, on "Fermat's Last Theorem and Related Topics in Number Theory." Professor Vandiver has devoted years to the ramifications of the theory that has grown up about the attempts to prove or disprove the theorem given by Fermat stating that there do not exist positive integers x, y, z, and n, $n > 2$, such that $x^n + y^n = z^n$. The intractability of this theorem along with the amazing fertility of the fields of algebra and number theory that have been opened by its consideration are among the most interesting facts in the history of mathematics. These colloquium lectures will take place on Tuesday, Thursday and Friday afternoons.

On Wednesday morning Professor G. Y. Rainich, of the University of Michigan, will address the society on "Product Integrals and their Applications to Geometry," and on Friday morning Professor G. T. Whyburn, of the University of Virginia, will give a paper "On the Structure of Continua."

The special feature of the program is the joint meeting of the society and the Institute of Statisticians. Papers on probability and statistics will be given and the meeting will also serve as a formal organization meeting of the institute, the preparatory work having already been done at an informal meeting and by committees.

The list of short papers contains some eighty titles, about half of these papers to be actually presented in person. These are synopses of their recent research by Americans in practically all the major fields of mathematics.

A joint dinner of all the organizations will take place on Thursday evening.

RECENT DEATHS

DR. CHARLES ELWOOD MENDENHALL, professor of physics and chairman of the department at the University of Wisconsin, died on August 18, at the age of sixty-three years.

DR. JAMES H. LEES of Iowa City died on August 6 at the age of sixty years. For twenty-eight years he had been assistant state geologist of Iowa.

DR. ELLWOOD C. PERISHO, since 1921 professor of geology at Guilford College, Greensboro, N. C., died on August 14. He was seventy-three years old. Before going to Guilford, Dr. Perisho taught at the University of Chicago, the State Normal School at Platteville, Wis., the University of South Dakota and the South Dakota College of Agriculture and Mechanic Arts. He was president of the South Dakota State College from 1914 to 1919.

DR. GEORGE HUGHES KIRBY, director of the New York State Psychiatric Institute and Hospital from 1917 to 1931 and formerly president of the American Psychiatric Association, died on August 11. He was sixty years old.

A CORRESPONDENT writes: "Thomas A. Bonser, curator of the Grace Campbell Memorial Museum of Spokane, Washington, died suddenly at his home Sunday evening, August 4, at the age of seventy-four years. Mr. Bonser was a graduate of Otterbein College and was given a master's degree at the University of Chicago. A student of plant ecology and local geology, ferns and mosses, his collections of Miocene flora of the Spokane region made possible Dr. Frank Hall Knowlton's work on that subject. Mr. Bonser's work in building a highly creditable museum in Spokane with a minimum supply of funds has made the entire northwest his debtor. At the December meeting of the Northwest Scientific Association he was elected vice-president and made the only honorary life member of that organization."

SCIENTIFIC NOTES AND NEWS

THE Regents of Education of South Dakota have appointed Dr. Joseph P. Connolly president of the South Dakota State School of Mines to succeed the late Dr. C. C. O'Harra. Dr. Connolly has been professor of mineralogy, petrography and economic geology at the School of Mines since 1919, and vice-president since 1926.

GENERAL ROBERT U. PATTERSON, of Washington, who will be relieved from active duty as surgeon-general of the army on August 28, after serving for four years, has been named dean of the Medical School of the University of Oklahoma and superintendent of the University Hospital. He will be succeeded as surgeon-general by Colonel Charles B. Reynolds.

SIR CUTHBERT WALLACE has been elected president of the Royal College of Surgeons, England, to succeed Sir Holburt Waring.

DR. ADOLPH M. HANSON, Faribault, Minn., who prepared active thymus and pineal extracts for experiments on the biologic effects of the extracts on rats, was awarded the medal of the Southern Minnesota Medical Association, presented annually during the meeting of the Minnesota State Medical Association, for his exhibit at the state meeting in Minneapolis, from June 24 to 26.

THE Ebert award, a gold medal, was presented to Dr. Marvin Andrews, professor of pharmacy at the University of Maryland, for a "meritorious scientific research paper" at the annual convention in Portland, Oregon, of the American Pharmaceutical Association. Dr. H. C. Christensen, of Chicago, was given a plaque in recognition of his services in handling exhibits at the Chicago World's Fair.

THE Baly Medal of the Royal College of Physicians has been awarded to Dr. F. H. A. Marshall as a pioneer in the experimental investigation of sex physiology and the relation of hormones to it. The Bisset Hawkins Medal has been awarded to Sir George Newman for his distinguished services to public health, and more particularly for the leading part played by him in the institution of social medical services.

PROFESSOR ARTHUS of Lausanne has been awarded the Monaco prize of 100,000 francs for his work on the physiology of poisons.

THE *Journal* of the American Medical Association reports that the Cancer Research Society of Japan has awarded its annual prize for 1935 to Dr. Tomizo Yoshida of the Sasaki Institute for his success in producing experimentally tumors in the liver.

PROFESSOR GREGORIO MARAÑÓN, of Madrid, has been elected a member of the Spanish Academy of Sciences, in succession to the late Professor Ramón y Cajal.

DR. ROBERT DEBRÉ, professor of bacteriology in the Paris Faculty of Medicine, has been elected a member of the Académie de Médecine in the Section of Hygiene in succession to the late Professor Léon Bernard.

THE following officers have been elected by the American Society for Testing Materials: H. S. Vassar, *president;* A. E. White, *vice-president;* and the following as members of the *executive committee:* W. H. Graves, R. L. Hallett, N. L. Mochel, H. H. Morgan and W. R. Webster.

DR. JOHN N. SIMPSON, who has been dean of the Medical School of West Virginia University since 1912 and a member of the faculty since 1902, has retired with the title of dean emeritus at the age of sixty-five years. The work of the deanship is being taken up by Edward J. Van Liere, M.D. (Harvard, '20), Ph.D. (Chicago, '27), who has been appointed acting dean. Dr. Van Liere has been professor of physiology and head of the department at West Virginia University since 1922.

DR. WALTER HUGHSON, professor of otology at the Johns Hopkins Medical School, has resigned to become director of the new otological research laboratory, especially designed for him at the Abington Memorial Hospital at Jenkintown, Pa.

DR. EDWARD MELLANBY, secretary of the Medical Research Council, has been elected Fullerian professor of physiology in the Royal Institution in succession to Sir Grafton Elliot Smith. It is expected that Professor Mellanby will give his first course of lectures at the Royal Institution in the autumn.

THE retirement is announced of Dr. Austin Cary, senior logging engineer of the Forest Service of the U. S. Department of Agriculture, with which he has been connected since 1910.

JOSEPH ROSSMAN, formerly of the U. S. Patent Office, has become patent counsel for the Marathon Paper Mills Company, Rothschild, Wis., where he will organize and conduct the Patent Department.

DR. EVERETT P. PARTRIDGE, supervising engineer of the Non-metallic Minerals Experiment Station of the U. S. Bureau of Mines, maintained in cooperation with Rutgers University at New Brunswick, N. J., has been appointed director of research of Hall Laboratories, Inc., at Pittsburgh, Pa. Dr. Partridge will be associated with Dr. Ralph E. Hall, the managing director

of Hall Laboratories, and his staff, with the scientific and technical specialists of Hagan Corporation, The Buromin Company, and Calgon, Inc., all of which are allied organizations, and also with the incumbents of the Industrial Fellowship on Calgonizing sustained by Calgon, Inc., at the Mellon Institute of Industrial Research.

OSCAR C. BRUCE, professor of soil technology at the University of Maryland, has leave of absence from the university to become manager of the newly established erosion-control project in Washington County. He will establish project headquarters at Hagerstown and will be directly in charge of the $200,000 demonstration project to be set up along Little Antietam and Israel Creeks in the northeast section of the county. The project, which will cover approximately 28,000 acres, is part of the national program of soil-erosion control. It will be the first of its kind undertaken in Maryland by the Soil Conservation Service.

DR. KENNETH E. CASTER has resigned his position as instructor in paleontology at Cornell University, but will continue his affiliation with the Paleontological Research Institution at Ithaca. He plans to carry on his paleontological and stratigraphic work on the Upper Devonian.

AN Associated Press dispatch reports that Dr. Alvin R. Cahn, of the department of zoology of the University of Illinois, has resigned after being connected with the university for thirteen years. It is reported that last spring Professor Cahn filed suits for $25,000 against two Illinois men, charging libel and defamation of reputation on account of statements printed and circulated by the defendants that reflected on his work as a teacher.

THE Committee on Scientific Research of the American Medical Association has made a further grant to Dr. John R. Murlin, University of Rochester, in support of his study on the influence of the male hormone upon metabolic processes. C. D. Kochakian, M.S., Boston University, is associated with Dr. Murlin in this work.

DR. BRUCE MAYNE, special expert of the U. S. Public Health Service in Columbia, S. C., has been appointed to represent the United States government at the International Congress on Entomology at Madrid in September. Formerly with the British Imperial Health Service, he also will represent the Malaria Survey of the Indian government. He plans, both in Madrid and at the conference of the Royal Society of Medicine in London, to show a one-reel moving picture of the Anopheles mosquito with a South Carolina setting.

THE United States has accepted the invitation of the Belgian government to be officially represented at the Fourth International Technical and Chemical Congress of Agricultural Industries, held at Brussels from July 15 to 28, and has designated the following delegates: Atherton Seidell, National Institute of Health; James M. Doran, Distilled Spirits Institute; and Charles N. Frey, Standards Brands, Inc.

A. A. OLSSON, of the International Oil Company and president of the Paleontological Research Institution, on returning recently from geological investigations in Colombia gave, on July 17, an informal lecture before the local members of that institution on the structure of the northern Andes, especially as displayed along a section north of Bogota from the Magdalena valley to the Llanos of Brazil. Discussions followed relative to the bearings of these new findings on the structure of adjacent countries, especially Venezuela, by Dr. and Mrs. Hodson (recently from this country) and others conversant with this portion of South America.

DR. HAROLD C. UREY, professor of chemistry at Columbia University, recently addressed students of the summer session at Teachers College, Columbia University, on "Some Recent Developments in Isotopic Chemistry." The meeting was open to the general public.

THE ninth International Physiological Congress, which has been meeting at Leningrad and Moscow, under the presidency of Dr. Ivan Pavlov, adjourned its sessions in Leningrad on August 17 and the members proceeded to Moscow. They were entertained at a banquet in the Kremlin palace, where they were addressed by Premier Molotoff. Professor A. V. Hill, of the University of London, vice-president of the congress, announced that the next meeting would be held three years hence in Zurich, Switzerland.

THE twenty-second French Congress of Hygiene will be held at the Institut Pasteur, Paris, from October 21 to 23, under the presidency of Professor P. Lereboullet; the subjects for discussion will be the hygiene and protection of infancy.

THE summer meeting of the Pennsylvania Academy of Science was held at East Stroudsburg on August 9 and 10. Between fifty and sixty members and guests attended. On the afternoon of August 9, Dr. E. M. Gress, Pennsylvania state botanist, led a trip to a typical quaking bog at Tannersville, where the characteristic flora of this environment was studied and specimens were taken. On Saturday morning Dr. Bradford Willard, of the State Geologic Survey, conducted a geological trip to the Delaware Water Gap and the region about the Stroudsburgs, with particular attention to the fossiliferous Devonian localities. A

short business meeting was held at the East Stroudsburg High School on Friday evening.

THE foundation of the Van't Hoff Fund has available for 1936 about 1,200 Dutch guilders to be used as endowments to investigators in the field of pure and applied chemistry who apply before November 1, 1935, to Het Bestuur der Koninklijke Academie van Wetenschappen, bestemd voor de Commissie van het "Van't Hoff-Fonds," Trippenhuis, Kloveniersburgwal, Amsterdam C, Holland. Applicants should send a detailed account of the proposed use of the grant and of the reasons on which they base their claim. In 1935 grants were made to the following: F. Feigl, Vienna; Georg Gorbach, Graz; Ph. Gross, Vienna; H. J. den Hertog, Deventer, Holland; D. P. Mom, Bandoeng; H. Raudnitz, Prague; I. J. Rinkes, Amsterdam; J. Tischer, Prague; Karl Weber, Zagreb; H. Willstaedt, Upsala, and L. K. Wolff, Utrecht.

UNDER the will of the late Arthur D. Little, who died on August 1, a controlling interest in the industrial research firm, Arthur D. Little, Inc., has been left in trust to the Massachusetts Institute of Technology. The will provides that Dr. Little's stock in the company is to be held in trust, with the income to go equally to the institute and to Mrs. Little. The trustees are instructed to develop with officials of the institute a plan whereby the firm may continue as an independent agency, conducted so as to benefit both industry and the institute. The trustees are Royal Little, of Providence, a nephew of Dr. Little; Francis R. Hart, president of the United Fruit Company, and Horace S. Ford, treasurer of the Massachusetts Institute.

LUKE WILSON, of Evanston, Ill., has deeded forty-five acres from his estate "Treetops," in Maryland, to the National Institute of Health to be used to raise small animals required for research work. A federal fund of $100,000 has been provided for the construction of the first building.

THE University of Michigan has received an anonymous gift of $25,000 which is to be placed at the disposal of the department of physics for development of research in the field of nuclear structure. The construction of a cyclotron and the installation of high potential equipment are planned. If artificially radioactive substances can be produced in sufficient quantity, these will be turned over to the medical staff of the university for the investigation of their possible therapeutic effects.

SIR JOHN D. SIDDELEY has made a gift to the University of Cambridge of the sum of £10,000 spread over a period of seven years, to help the development of aeronautical research and to assist the work of Professor Melvill Jones and his associates in the subdepartment of aeronautics in the university. No specific conditions are attached, but it is suggested that it may be found best to allow a considerable proportion to accumulate to form a capital endowment and to use the remainder for immediate purposes.

LORD NUFFIELD has given £16,000 for the purposes of the new institute for medical research at the University of Oxford. This is additional to the Radcliffe Observatory buildings and their surrounding land, which he bought when it was proposed to remove the observatory to South Africa. The institute is now to be called the Nuffield Institute for Medical Research.

MRS. MOSES P. EPSTEIN, of New York, acting president of Hadassah, the Women's Zionist Organization of America, has announced that the sum of $106,000 has been contributed to the building fund of the Rothschild-Hadassah-University Hospital, which will be built in Jerusalem by Hadassah and the American Jewish Physicians' Committee. Preliminary architectural plans are now being completed in Palestine and will be studied by the Palestinian and American members of the building committee, of which Dr. J. J. Golub, director of the Hospital for Joint Diseases, New York, is consultant. The medical center will be the first of its kind in Palestine and is intended as a model teaching and research institution for the entire Near East. On its hospital and teaching staffs will be a number of exiled German specialists, including Professor Bernhard Zondek, gynecologist, and Professor Ludwig Halberstadter, specialist in cancer. The medical center, which will be erected on a 25-acre plot on Mt. Scopus overlooking the city of Jerusalem, will include a 300-bed hospital, a post-graduate school of medicine, research laboratories and a nurses' training school.

A FOUR-STORY annex to the museum on the estate of William K. Vanderbilt, at Northport, Long Island, which houses the largest privately owned marine collection in the world, will be erected in the fall in memory of William Kissam Vanderbilt, Jr.

ACCORDING to a recent Associated Press dispatch, President Roosevelt has allotted the sum of $3,450,000 of work relief funds to the Public Health Service for a survey of chronic diseases. Surgeon-General Hugh S. Cumming is said to have estimated that the study would give a year's employment to 3,500 people now on relief rolls. The project will include: A house-to-house canvass in selected urban and rural communities to ascertain the prevalence of long-standing illnesses among rich, poor and middle class families. Physical examinations in a few instances to check the ac-

curacy of the canvass reports. A survey of medical facilities, particularly for chronic diseases.

PRESIDENT ROOSEVELT has approved a $10,000 allotment of federal funds for a survey of the big trees in Sequoia National Park, Calif., by the Works Progress Administration, the money to be spent by the National Park Service.

AN interdepartmental committee to coordinate health and related welfare activities of the government, in line with the new Social Security Act was established by President Roosevelt on August 15. The President's statement reads: "In view of the passage and signing of the Social Security Bill there is increasing necessity for better coordination of the health activities of the Federal Government. I am, therefore, creating at this time an interdepartmental committee to give attention to this subject. As members of this committee I have appointed the following government officials: Josephine Roche, Assistant Secretary of the Treasury, chairman; Oscar Chapman, Assistant Secretary of the Interior; M. L. Wilson, Assistant Secretary of Agriculture, and A. J. Altmeyer, Second Assistant Secretary of Labor. I am directing this committee to include within the scope of its work not only health activities, but closely related welfare activities as well. As its immediate task I am instructing this committee to assume responsibility for the appointment of special committees to be composed of physicians and other technically trained persons within the government service to study and make recommendations concerning specific aspects of the government's health activities. I am confident that this procedure will facilitate the consummation of a series of appropriate cooperative agreements among the various departments of the government. I am also hopeful that in this way we can eventually bring about a complete coordination of the government's activities in the health field."

DISCUSSION

MINNESOTA MAN—A DISCUSSION OF THE SITE

IN a recent and illuminating discussion Antevs[1] has given a possible migration route between the Cordilleran and Keewatin Ice Sheets in the early part of the last glacial retreat. Through this route he believes that men found their way into the Great Plains area and thence spread into the remainder of the Continent some 20,000 or perhaps 15,000 years ago. He believes that they had no early precursors, but he does not question the existence of the "Folsom point-Yuma blade complex." He implies that the makers of these points might have followed the postulated migration route, as the deposits in which these relics have been so far found are generally considered postglacial, although the proof is not final or conclusive.[2]

Minnesota Man, however, occurs in silt of presumably somewhat greater antiquity.[3] Thus troublous questions are raised. Now Antevs disposes of these questions by throwing doubt upon the true association of the skeleton with the silt deposit in which it is apparently contained. He says:[4] "However, both the sample of the silt and photographs, which the writer has seen through the courtesy of Dr. G. A. Thiel, show that the silt bed is disturbed, and this raises the probability that the person was buried by a landslide long after the formation of the silt." The details of proof and the larger features of this important find can well be left to the complete monograph which Professor Jenks expects to publish this fall. Here I wish merely to discuss the possibility of landsliding at or near this site.

Through the kindness of Professor Jenks and under his guidance I visited on June 23 the site at which the skeleton known as Minnesota Man was found, on U. S. Highway No. 59. Franklin T. McCann accompanied me, and P. F. Stary and Carl Steffen joined us at Detroit Lakes.

The site is a road cut about three miles north of Pelican Rapids and near the north end of Prairie Lake, where Pelican River enters. Here the ground rises in gentle rolling slopes from the elevation of Pelican River at 1,313 feet to the top of the cut at 1,336 feet. On the line of the road grade the distance is 650 feet. The average gradient of the somewhat irregular natural slope is 3.5 feet in a hundred. As the road crosses the river on an elevated grade, the road grade through the cut is much gentler. The skeleton was found beneath the road grade about a hundred feet south of the high point of the hill and in the direction away from the river. This southerly slope leads with equally gentle grades to a shallow valley beyond which rises a still higher hill in which the highway again lies in a cut.

The silt layers are of the coarsely varved type and practically horizontal as seen in the steep walls of

[1] Ernst Antevs, *The Geographical Review*, 25: 2, 302–309, April, 1935.

[2] Kirk Bryan, *Geol. Soc. Amer. Bull.*, 40: 128–129, 1929; E. B. Howard, SCIENCE, 78: 524, 1933; A. E. Jenks, SCIENCE, 80: 205, 1934.

[3] A. E. Jenks, SCIENCE, 75: 607–608, 1932; *Proc. Nat. Acad. Sci.*, 19: 1–6, 1933.

[4] E. Antevs, *idem.*, p. 305.

the cut on either side of the site. There is a humus soil zone ("A" horizon) six inches to a foot thick and below it an amorphous "B" horizon to a total depth of between three and four feet. This "B" horizon shows some lime accumulation at the base and there are a few veins of limey material extending down into the underlying laminated silt. These soil zones conform to the contour of the hill and from the top of the hill down the slope cut successive layers of silt. As each layer comes into the soil zone it is slightly distorted, but there is no evidence of sliding or of pronounced movement either of the soil or of the underlying layers of silt. On slopes as low as are characteristic of this little hill rapid or violent movement of the soil can not be expected, even under the relatively severe frost action of Minnesota winters.

The silt deposit covers several square miles and is eroded into gentle hills and valleys. The Pelican Rapids topographic sheet of the U. S. Geological Survey shows that the highest points lie at elevations of 1,380 to 1,390 feet. On the map the hills appear to be flat-topped and the depressions rounded and mostly enclosed holes. One thinks immediately of a plain pitted with ice-block holes. Whatever the origin of the depressions, the hill slopes are molded by weathering and rain wash. In this process shallow gullies have been opened and then filled. One of these filled gullies crosses the road in the cut south of the site. It has a V-shaped cross-section four to 5 feet deep and twenty to thirty feet across. The filling is of reworked unlaminated silt with small nodules and veins of lime carbonate below a humus zone deeper than usual. Such filled gullies are not uncommon and would permit the burial of objects later than the silt to depths of five feet. There is no evidence that such a gully ever existed in the hill in which the skeleton was found and the differences between the filling of these gullies and the normal laminated silt are so great that no experienced person could confuse the two.

I have also examined the photographs taken by Professor G. A. Thiel. They illustrate the present condition of the cuts and have a slightly deceptive aspect. One taken in the cut south of the site shows what superficially appear to be slight offsets in the laminae of the silt. These banks have now been exposed to the weather for more than two years without being retrimmed. Parallel to the face of the cut there is a skin of frost-heaved material from two inches to a foot thick. This can easily be peeled off and the laminae then appear as continuous and smooth lines.

The silt of this locality rests on sand and has a slightly undulatory contact on the sand. The contact appears to rise toward the south and, whereas it lies below the road grade at the first cut, it rises above grade at the second or southern one. These undulations are also well shown in large road-cuts about seven miles southeast on the shores of Lake Lida near Oak Lodge. Here the silt rests unconformably on yellow till whose surface was evidently the hilly eastern boundary of the lake on which the silt was deposited. The silt dips away from the hills, and its deformation may be attributed to differential compaction. Whether all the undulations of the silt can be so attributed can only be determined by intensive fieldwork.

At this locality also there are narrow steep-sided gullies which cut both till and silt. The side slopes range from ten to thirty degrees. Adjacent to these hill slopes the silt is faulted in successive faults each with a throw of two to three feet. These faults are obvious relics of landslides, but the slopes on which they occurred are many times greater than those of the small hill within which the skeleton was found.

The positive evidence that the skeleton lay about nine feet below the surface and below undisturbed silt laminae has been assembled by Professor Jenks. I had the opportunity of talking to Carl Steffen, the workman whose keen eye detected the shell ornament and who uncovered the skeleton. Mr. Stary, the engineer in charge, was also present. The testimony of these intelligent men that the skeleton was found below undisturbed silt, the laminae of which were clearly visible to their accustomed eyes in the smooth slope of the shallow V-shaped cut made by the grader, can not be lightly disregarded.

In contrast, my brief inspection provides negative evidence. In the vicinity of the site there are no geologic phenomena in sight or processes in action that afford an indication of or reasonable probability of landsliding or similar disturbances which would lead to the intrusive deposition of the skeleton into the silts. The age of the silts is, therefore, critical and will be adequately treated in the forthcoming report by Professor Thiel, who has fitted the deposition of this silt into the glacial history. The undulations of the silt, its considerable dissection by streams, the peculiar topography of its enclosed depressions, its deep soil all testify to a measurably greater antiquity than the silt beds of nearby Lake Agassiz.

KIRK BRYAN

HARVARD UNIVERSITY

THE OCCURRENCE OF ANOPHELES MACULIPENNIS IN MEXICO

ACCORDING to Berber, Komp and King[1] and Barber and Forbrich,[2] *Anopheles maculipennis* Meig. is com-

[1] *Public Health Reports*, xliv, No. 22, pp. 1300–1313, Washington, D. C., May 31, 1929.
[2] *Ibid.*, xlviii, No. 22, pp. 610–623, June 2, 1933.

mon in New Mexico, where it is the chief malaria carrier, occurring in the Rio Grande and San Juan Valleys, up to an altitude of 5,600 feet. It is therefore surprising that this species has not been reported for the northern part of the adjacent Mexican State of Coahuila, where several Culicids of northern origin as *Aedes vexans* Meig. and *A. dorsalis* Meig. have been found and where climatic conditions are very similar to those of New Mexico. Also in Dr. Martini's paper,[3] which the Mexican Public Health Department is just publishing, *A. maculipennis* does not appear in the list of Mexican Anophelids.

In spite of these negative data, I have to announce that the so-called *A. maculipennis,* undistinguishable in the male hypopygia from California and British Columbia specimens, occurs throughout the whole Mexican tableland, reaching the Valley of Mexico. It has apparently been confused by former authors with *A. quadrimaculatus* Say. This finding, which extends the area of distribution of the species on the American Continent for nearly 14 degrees to the south and into the tropics, has a special interest in view of the recent European controversies on the so-called races of *A. maculipennis.* The writer is of the opinion that the European maculipennis is composed of at least two valid species, *A. maculipennis* type with var. *messeae* and var. *melanoon,* and *A. labranchiae* with var. *atroparvus.* The American species belongs, according to the hypopygium of the male, not to *A. maculipennis,* but to *A. labranchiae,* as shown in 1933 by Martini,[4] but has distinctive characters in the egg, which would justify retaining it as a separate species, for which the old name *Anopheles occidentalis* Dyar and Knab should be used. Should it result that the division between the American and European form is only of subspecific rank, then the European form would bear the name *A. occidentalis* var. *labranchiae.*

A more extensive paper will be published in the *Revista Mexicana de Biologia.*

ALF. DAMPF

ENTOMOLOGICAL LABORATORY
MEXICAN PUBLIC HEALTH
DEPARTMENT

EGGS OF A PENEID SHRIMP

SINCE Fritz Müller,[1] in 1863, published his excellent Brazilian observations on the metamorphosis of the prawns, students of the Peneidae have long been interested to know more of the character of the eggs and the early nauplii of this group of Crustacea. The researches of Brooks,[2] Kishinouye[3] and lately of Heldt[4] have done much to supplement the work of Müller. Recently the writer, during the course of a study of the early life history of the commercial American prawns or shrimps, *Penaeus setiferus* and *Penaeus brasiliensis,* secured a number of shrimp eggs, most probably of the species *P. setiferus.* These eggs were spherical in shape and possessed an extremely thin delicate membrane. The diameter of the eggs ranged from .38 to .42 millimeters. Within each otherwise transparent egg rested a well-developed nauplius, the length of which ranged from .21 to .26 millimeters. The nauplius was approximately one half the diameter of the egg.

These eggs were secured by a meter tow net at the surface of the sea near the sea buoy off Jekyl Island, Georgia, on June 17, 1932, by the scientific staff of the U. S. Bureau of Fisheries. The same plankton haul also yielded free-swimming nauplii of the same size and stage as those observed within the eggs and apparently added one earlier stage of free-swimming nauplius to that presented by Müller. Nauplii of approximately the same size and stage as described by Müller (.4 millimeter) were also taken.

Several hundred nauplii and zoae of the commercial shrimps, *P. setiferus* or *P. brasiliensis,* taken along the South Atlantic and Gulf coasts during the past three years, provide an interesting series of growth stages and with the addition of the shrimp eggs assist considerably in an understanding of the spawning of the commercial shrimps and the distribution of the young in inshore waters off the coasts of South Carolina, Georgia, Florida and Louisiana.

JOHN C. PEARSON

U. S. BUREAU OF FISHERIES
NEW ORLEANS, LA.

AN ANOMALOUS MUSCLE IN THE CALIFORNIA RIVER OTTER

IN a study made recently of the osteology and myology of *Lutra canadensis brevipilosus* the muscle described below was discovered in one specimen, a female, and found to occur on one side only. This muscle was found on the left side without the slightest trace to be found of a similar muscle on the right side.

The muscle arises as a slender round tendon on the anterior and ventral border of the ilium and continues ventrally and then posteromedially as such for a distance of about 4.0 centimeters, which brings it to the level of the medial posterior border of *M. sartorius.* The round tendon quickly broadens out into the fleshy part, which is 2.7 centimeters long and 0.64 centimeters wide, and quite thin. The fleshy part tapers

[3] "Los Mosquitos de Mexico." Boletines Técnicos, Serie A. No. 1, Del Departamento de Salubridad Pública, Mexico (in press).

[4] *Proc. Ent. Soc. Washington,* 35, No. 5, p. 65.

[1] R. Muller, *Arch. f. Naturgesch.* 29, Bd. 1863.

[2] W. K. Brooks, Johns Hopkins Univ. Circ., Vol. II, 1882.

[3] K. Kishinouye, *Zoologisches Anzeiger,* XXIII, 1900.

[4] H. Heldt, Compt. Rend. Acad. Sci. (Paris), 1931.

some, ending in a broad flat and somewhat stiff tendon of insertion 2.74 centimeters long.

The slender round tendon of origin passes along the line of origin of *M. sartorius* on the crest of the ilium. The fleshy part and one centimeter of the flat tendon lie free amongst the layers of loose fascia so common in this region. Fleshy origin fibers of *M. gracilis* arise along the posterior 1.7 centimeters of the flat tendon, and for 1.2 centimeters of this from the tendon alone, the origin then shifting to the pubis. The flat tendon inserts on the anterior and ventral border of the pubis immediately lateral to the pubic symphysis. The position of this singular muscle suggests either a modified or abnormal Poupart's ligament.

EDNA M. FISHER

UNIVERSITY OF CALIFORNIA
BERKELEY

THE EFFECT OF PROLACTIN ON THE ESTRUS CYCLE OF NON-PAROUS MICE

THE mammary milk secretion is governed by a specific pituitary hormone which is independent of the growth- and gonad-stimulating hormone of the pituitary. It was first isolated by Riddle, Bates and Dykshorn[1] and named prolactin. Prolactin does not affect the mammary glands of normal adult guinea pigs or rabbits, unless they have been previously prepared for about three weeks with theelin and progestin. Moreover, it acts when injected in similarly prepared male or female animals that have been castrated or hypophysectomized. Crew and Miskaia[2] noted that the length of the lactation interval (from the estrum after parturition to the estrum at the close of lactation) extends for from 20 to 25 days. The question arises whether this delay in estrum is caused by the corpus luteum or the pituitary hormone prolactin. If this former were true, the injection of prolactin should not influence the estrus cycle in the non-parous animal.

Accordingly, the estrus cycle of 30 mature young female mice was studied over a period of one month. At the end of that time, 14 mice, whose cycles had been absolutely regular, were selected. These 14 mice were injected subcutaneously with one bird unit of prolactin[3] daily, over a period of 30 days. Daily examinations showed that no changes occurred in the mammary glands as the result of the prolactin. Twenty-four hours after the prolactin injections were begun, the estrum became suspended. Daily vaginal smears from all mice showed no estrum during the following 20 to 25 days. It reappeared after this period of 20 to 25 days in spite of further continued injections of prolactin, and was markedly prolonged, continuing from 4 to 8 days. During these days the vaginal smears showed only non-nucleated epithelial cells.

These observations may be summarized: In the mature, nonparous mouse prolactin suspends the estrus cycle for about three weeks, after which a prolonged estrum sets in lasting from 4 to 8 days in spite of further continued injections. It would appear from this observation that the suspension of the estrus cycle during lactation is caused by the pituitary hormone prolactin, rather than a hormone from the corpora lutea.

IRMGARD DRESEL

THE SCHOOL OF MEDICINE
THE GEORGE WASHINGTON
UNIVERSITY

SCIENTIFIC BOOKS

FARADAY

Faraday's Diary. Edited by THOMAS MARTIN, M.Sc., and published by order of the Managers of the Royal Institution of Great Britain, with a Foreword by Sir William H. Bragg, O.M., K.B.E., F.R.S. G. Bell and Sons, Ltd., London. Vols. III, IV, V.

VOLUMES I and II of this great publication were reviewed in SCIENCE of January 13, 1933. Two more volumes are to follow. The books will be sold only in sets, of which 750 copies will be issued. The price of the set is twelve guineas.

The volumes now in hand show the same careful transcribing and editing as the earlier ones. They are beautifully printed and bound. The editor, the managers of the Royal Institution and the publishers are to be again congratulated on the further progress of this noble memorial.

In Volume III Faraday records the progress of his research on electrostatic induction, the earlier part of which was recorded in the previous volume. He was particularly interested in proving that induction could act along curved lines, similar to the curved lines of magnetic force. When he was able to show this experimentally he was led to the belief that these lines of force were evidence of a polarized condition of the medium between the two conductors. He was then led to think that some differences in inductive power might be shown if different media were used to transmit the inductions and so to the discovery

[1] *Amer. Jour. Phys.*, 105: 190, 1933.
[2] Allen, "Sex and Internal Secretion."

[3] The prolactin used was furnished by the Research Department of E. R. Squibb and Sons.

of the specific inductive capacity of dielectrics. The experiments by which this result was reached were extremely difficult to carry out, and subject to many sources of error, but these were finally overcome, and Faraday at last felt justified in recording the conclusion in note 4184 that "From the above and the other results, I cannot resist the impression that there *is a difference of inductive capacity in body.* I do not see how it can be explained away, though I try all I can for that purpose."

The rest of this volume is filled with records of experiments on the electric discharge in different gases, which led to no important conclusions; on the electric properties of the gymnotus; and on the origin of the electric current in voltaic cells, which Faraday ascribed to chemical action in opposition to the contact theory of Volta.

This last study runs over into Volume IV, but the entries are less numerous than in the earlier volumes. There are very few in 1840 and there is a gap of more than a year in which nothing is recorded. Faraday's strenuous labors had exhausted him. He was troubled with fits of giddiness and loss of memory, for the cure of which he was ordered a complete rest. To some extent he recovered his strength and was able to work again, but his defective memory still persisted, and indeed became more pronounced as the years went on, so that at least in one case he found when he had finished a long series of experiments that he had covered the same field eight months before. Faraday began work again in January, 1842, on the production of electric charge by steam issuing in a jet, a fact which had been discovered by Sir W. Armstrong. There is a gap of a year from February, 1843, to February, 1844, before he took up anything else, and then he returned to his earlier work on the liquefaction of gases, which he carried on with a certain measure of success, though he never attained the goal which he sought, the liquefaction of oxygen, nitrogen and hydrogen.

In the year of Faraday's inactivity Joule published his first paper on the mechanical equivalent of heat. The question of the "Correlation and Conservation of the Physical Forces" began to be discussed. Faraday saw in this question a field for experimental investigation, and much of his work from then on is concerned with this problem. He first set out to discover some relation between light and electricity, by sending a polarized ray through an electrolyte. He found no effect on the light. Nor was there any effect when the light was sent through various transparent bodies under electric stress. He then turned to magnetism, and after many trials with various transparent bodies without success, he finally introduced into the magnetic field a block of his heavy glass. In many positions of the glass in the field he found no effect. But, when contrary magnetic poles were on the same side, there *was an effect produced on the polarized ray,* and thus magnetic force and light were proved to have relation to each other."

After spending two months in the search for other bodies possessing this property and the proof that the effect was a rotation of the plane of polarization, Faraday suspended a short block or rod of his heavy glass in the field of a powerful electromagnet and found that it swung to point itself equatorially or across the lines of magnetic force. He had thus discovered diamagnetism. By an analysis of the phenomena he proved that the bodies which he called diamagnetic moved from the stronger to the weaker parts of the magnetic field, in contrast to magnetic bodies, which move in the opposite sense. This was Faraday's last great contribution to experimental physics.

In the following years Faraday investigated the magnetic properties of many substances and studied the peculiar action known as magnecrystallic. He tried to find some way of producing the electric current by the action of polarized light, without result.

In Volume V is recorded his famous attempt to connect gravitation with electricity, in which he also failed. In this volume appears also his experimental study of the lines of force about a magnet, which led him to a clearer conception of their properties. With this work the volume closes.

Faraday. By THOMAS MARTIN. "Great Lives." Duckworth, London. pp. 144.

THE author of this little book is the editor of the monumental edition of Faraday's Diary, which is now being issued as a memorial to that great experimental philosopher. He is in position to write with authority. The outline sketch of Faraday's life and work is exceedingly well done. The book is interesting and, within the limits permitted to the author, complete. One can see that his long acquaintance with Faraday's records of work has given him a vivid conception of Faraday's character and mental processes. The book is an excellent example of a short biography.

W. F. MAGIE

PRINCETON UNIVERSITY

APPLIED ENTOMOLOGY

Applied Entomology—An Introductory Text-book of Insects in Their Relation to Man. By H. T. FERNALD. Third edition, viii + 403 pp., 384 illus. McGraw-Hill Book Company, Inc., New York and London, 1935. $3.50.

THE Massachusetts College of Agriculture at Am-

herst has long been known as the trainer of very many applied entomologists of high rank. Once, in an address, I discussed the subject of the education of the entomologists in the federal service and I found that many of the best of them had studied under the Fernalds. And so when the first edition of this book was published in 1921 I greeted it with great interest, knowing that from it I should find out something of the way in which these good men had been taught.

This last edition, just published, contains much new matter, and much of the rest has been rewritten since the second edition was published in 1926, and the last ten years have been especially noticeable for advances in the fight against insects as well as in the new problems that have confronted the rapidly increasing army of workers.

The dedication of this edition appeals to me especially. It reads: "To the Memory of my Father, Professor Charles H. Fernald; one of the first teachers of Economic Entomology to College Students in this Country." I knew the elder Fernald well. He was a truly great teacher and he will be remembered for many years. Henry, the author of the present volume, had greater educational advantages than his father (I remember that he studied at Johns Hopkins fifty or more years ago under W. K. Brooks and his colleagues) and greatly profited by these advantages as well as by inherited aptitude and constant association with his father. His whole career was spent at the college, and he constantly mixed with the leaders in the federal and state services and was at one time the president of the big association of economic entomologists.

This new edition is admirable. I marvel at its scope and thoroughness, and I marvel at the wonderful way in which the author has concisely put such a mass of information. No one, with the least tendency to ramble, could have told the stories of the cotton-boll weevil, the San Jose scale, the gypsy-moth and the other great pests as Fernald has done, competently, concisely and readably. And the book could not have been done until to-day. On examining it, old-timers, like myself, must say to themselves, "Oh, if I could only have had a book like this when I was young!" But there could have been no such book then. The good old times were not so good after all in many ways. Of course we old fellows after such a thought as that shrug our shoulders and grumble, "Well, they were not so bad either in many other ways."

But to the book: There are four chapters on the place of insects among other animals and on their structure and development; one on nature's control methods; four on man's method of control; one on the relationships of insects; 23 on the different orders, and a final chapter on the animals, not insects, with which the entomologist is expected to deal—a necessary chapter, since it includes ticks and mites, eel worms, millipedes and so on.

The 23 chapters on the different orders contain accurate, condensed, but sufficient information upon the different injurious species with a statement as to remedial treatment in each specific case; and all these can be readily traced from the very competent index.

The make-up of the book is excellent. It is of convenient size and is fully and admirably illustrated. Think of 384 illustrations to 384 text pages! Many of these illustrations are original and the others are borrowed from other good books. The selection of the latter has been very careful and shows a very wide reading on the part of the author.

For some years now, Dr. Fernald, having retired from teaching, has been living for most of the time at Orlando, Fla., which has now become rather a center for entomologists. There he has worked away almost uninterruptedly on his rewriting of much of the second edition in constant touch with W. W. Yothers, W. V. King and other well-known workers whose advice and help he acknowledges in his readable preface.

I congratulate Dr. Fernald very heartily. I can see that this book will be of great value not only to teachers and students, but to every one who even temporarily wishes to know the answer to some question about injurious or beneficial insects. I shall give the book to the library of the old country club in the Catskills where I am writing this, since many of the families have beautiful gardens and there are many children growing up with most inquiring minds. I predict that it will be read and reread.

Its admirable composition and its thoroughness explains to me in a large part the high rank of the entomologists who have come from that laboratory of the Massachusetts Agricultural College.

L. O. HOWARD

SPECIAL ARTICLES

X-RAY REFLECTIONS OF LONG SPACING FROM TENDON

THE proteins which have given crystalline x-ray diffraction patterns fall into two groups. One—the soluble proteins that can be grown in recognizable crystalline forms—give the long spacings to be expected from true crystals composed of very large molecules. Pepsin,[1] hemoglobin[2] and insulin[3] belong

to this class. Tendon and hair are examples of the second, insoluble, group of crystalline protein structures. They provide typical fiber diffraction patterns upon which no large spacing reflections have hitherto been found. From the apparent absence of such spacings it has often been suggested that these animal fibers do not consist of large molecules in typical crystalline array but rather of clusters of indefinitely prolonged polypeptid chains bearing side chains irregularly distributed along them. This type of structure and the x-ray evidence bearing on it have been extensively discussed by Meyer and Mark,[4] by Katz,[5] by Astbury[6] (especially for wool and hair), and by many others.

We have been interested in tendon and other forms of connective tissue as typical examples of these insoluble crystalline proteins and have made experiments to see whether they really differ from the soluble proteins in giving only short spacings. For the photographs about to be described raw tail tendon of the kangaroo has been used because it yields especially well-oriented fiber patterns.[7]

By employing a camera of sufficient radius in conjunction with a slit system composed of small pinholes, spacings greater than the previous maximum of ca 11A can be photographed. A tracing of such reflections of chromium radiation recorded in an 11.4 cm radius camera is reproduced in Fig. 1. The observed spacings, as yet only approximately determined, are listed in Table I.

FIG. 1. A tracing of the inner reflection pattern of tendon. Letters refer to spots recorded in Table I.

There is every reason to expect that still longer spacings will be found with bigger cameras and finer slits. It is obvious that detailed knowledge of the structure of tendon must await a thorough exploration of this region of large spacings. The mere existence of long spacings, however, makes it certain that tendon cannot consist of parallel polypeptid chains bound together by irregularly repeated cross linkages. Instead, there is at present no sound reason for considering tendon, and undoubtedly other forms of connective tissue as well, as having anything but a typical crystalline array with all the regularity of atomic arrangement this implies. Two possibilities then remain. According to one a tendon, like a crystal of a soluble protein, consists of a regular assemblage of very large molecules, all of equal size. On the other hand, it might be built of indefinitely extended polypeptid chains along which different amino-acid residues were regularly repeated with a master period of a hundred or more Angstrom units. Such a model, which is an elaboration of that often assumed for cellulose, is not a grouping of like molecules: the molecule is identical with the crystal fragment. A choice between these structure types can undoubtedly be made when more data are available. In the meantime the existence of large spacings from tendon makes desirable a careful search for similar spacings from cellulose and other macromolecular fibrous substances.

TABLE I

LONG SPACINGS OBSERVED IN KANGAROO TENDON

Spot	Intensity	Spacing
B (Fig. 1)	f	7.33A
A "	ss	10.83
Fiber axis spot	ff	21.7
"	m	33.6
"	f	53.1
"	s	68.9

Note: If these four spots on the fiber axis are different orders of the same reflection, as is conceivable, they are the 5th, 6th, 10th and 15th orders of a fundamental spacing of ca 330A. Patterns of other forms of connective tissue also show a horizontal reflection (inside of A) with a spacing of ca 23A.

SUMMARY

A series of large spacings has been observed in diffraction photographs from tendon. The significance of this observation for the structure of this and other fibrous macromolecular substances is briefly discussed.

RALPH W. G. WYCKOFF
ROBERT B. COREY
J. BISCOE
ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK, N. Y.

[1] J. D. Bernal and D. Crowfoot, *Nature*, 133: 794, 1934.
[2] R. W. G. Wyckoff and R. B. Corey, SCIENCE, 81, 365, 1935.
[3] D. Crowfoot, *Nature*, 135: 591, 1935.
[4] K. H. Meyer and H. Mark, "Der Aufbau der hochpolymeren organischen Naturstoffe," Leipzig, 1930.
[5] J. R. Katz, "Die Röntgenspektrographie als Untersuchungsmethode," Berlin, 1934.
[6] W. T. Astbury, "Fundamentals of Fiber Structure," London, 1933.
[7] We are indebted to Dr. Ralph O. Clock of Davis and Geck, Inc., for supplying us with this material.

FURTHER STUDIES ON ORAL IMMUNIZATION TO COLDS

IN a previous report[1] we gave our results obtained during the winter of 1933–34, in the prevention of colds by oral administration of a cold vaccine which was high in heterophile antigen. In that work, 462 persons who took the vaccine orally showed a decrease of 57 per cent. in the incidence of colds, whereas 527 controls showed a decrease of only 12 per cent. This amounts essentially to a decrease of 45 per cent. due to the oral vaccine.

This last winter, 1934–35, we have given the oral cold vaccine to 445 persons and observed 469 others as controls. The results are shown in the table.

RESULT OF STUDIES OF IMMUNIZATION TO COLDS BY ORAL VACCINE FOR WINTER OF 1934–35

	W. S. Life Ins. employees		Medical students		U. C. Life Ins. employees		General group		Nurses		Total	
	Took vac.	Controls	Took vac.	Controls	Took vac.	Controls	Took vac.	Controls	Took vac.	Controls	Took vac.	Controls
*No. cases	87	100	80	87	31	48	171	201	30	33	399	469
Average total number colds per year in past three years	291	176	296	264	98	77	768	555	101	64	1554	1136
Total number colds experimental year ..	97	119	87	223	52	59	185	385	44	51	465	837
Decrease in number of colds ..	194	57	209	41	46	18	583	170	57	13	1089	299
Per cent. decreased	66.6	31.2	70.6	15.5	46.9	23.4	75.9	30.6	56.4	20.3	70.0	26.3

*Forty-six cases who reported continuous colds in previous years, although taking the vaccine, this year were not included in the figures of this table. These forty-six cases can be summarized as follows; three were not helped, they still had continuous colds; forty-three stated they were greatly benefited, reporting a total of thirty-four colds this winter for the forty-three individuals.

Ninety-four cases who started the vaccine but only took the vaccine for a few days or several weeks are not included in this figure.

Although all heterophile antigens have similar properties, there is sufficient evidence to indicate that homologous heterophile antigens and antibodies have a greater affinity for each other than heterologous[2] ones. Hence the oral heterophile cold vaccine which started as a combination of the pneumococcus DR I, and streptococcus has been improved by the addition of other bacteria which infect the respiratory tract. The strains were selected for their heterophile content and their ability to resist the effects of the gastrointestinal secretions. Additional strains of pneumococci were also used. The bacterial cultures were sterilized, the bacteria separated, absorbed on starch, dried and finally filled into capsules. Each capsule contained pneumococci 25 billion, *H. influenza* 5 billion, streptococci 15 billion and *M. catarrhalis* 5 billion.

It is necessary that the vaccine be taken with cold water on an empty stomach, as otherwise the action of the stomach juices on the vaccine prevents the absorption of the complete antigen. Frequent administration of the vaccine is also essential, since the resultant immunity is of very short duration.[3] For these reasons the treatment consisted of the ingestion of one capsule with a half glass of cold water at least one half hour before breakfast for seven consecutive mornings, after which one to two capsules per week were taken throughout the season.

Reactions following the use of the oral vaccine occurred occasionally, and these were usually in persons who started taking the vaccine just after recovering from a cold. The reaction manifested itself as a grippy feeling or a mild intestinal discomfort.

SUMMARY

(1) Among the 445 persons taking the vaccine, 399 had 1,089 (70 per cent.) less colds this year than usual, whereas the 469 controls showed a decrease of only 299 (26.3 per cent.) colds, an essential decrease of 43.7 per cent. due to oral cold vaccine.

(2) It was stated by 326 (81.7 per cent.) of the 399 persons taking the vaccine that they had been greatly benefited.

(3) Of forty-six persons who had previously been troubled with practically continuous colds, three reported that they were not helped while taking the vaccine, while the remaining forty-three, suffering a total of only thirty-four colds during this winter, were

[1] George E. Rockwell, Herman C. Van Kirk and H. M. Powell, *Jour. Immunol.*, 28: 475, 1935.

[2] C. H. Bailey and M. S. Shorb, *Amer. Jour. Hyg.*, 17: 358, 1935; R. Landsteiner and P. Levine, *Jour. Immunol.*, 22: 75, 1932.

[3] George E. Rockwell and Herman C. Van Kirk, *Jour. Bacteriology*, 29: 47, 1935.

greatly benefited. In other words, these forty-three persons, previously in a state of practically continuous coryza, suffered from less than one cold per person during this season.

(4) The oral vaccine makes frequent administration practical, which is so essential in such short life immunities as occur with the bacteria of upper respiratory infections.

GEORGE E. ROCKWELL
HERMANN C. VAN KIRK
DEPARTMENT OF BACTERIOLOGY
UNIVERSITY OF CINCINNATI
H. M. POWELL
LILLY RESEARCH LABORATORIES
INDIANAPOLIS, INDIANA

A "GROWTH SUBSTANCE"

IN connection with a survey of the nutritional requirements of pathogenic yeasts and molds being carried on in this laboratory in collaboration with Dr. L. B. Kingery, of the Department of Dermatology, University of Oregon Medical School, we observed the case of an organism isolated from a deep skin lesion, which the authors decided to investigate more fully.

The organism grows with extreme rapidity in a suitable medium, is easily suspended and handled and is reasonably uniform in its responses. Aside from the ordinary nutrients used for yeast culture[1] this organism requires an assortment of amino-acids and is stimulated appreciably both by pantothenic acid and crystalline vitamin B. To promote rapid growth, however, there is required in addition another water-soluble substance which is particularly abundant in liver, liver extract No. 343 (Eli Lilly), kale and alfalfa, and to a lesser but considerable extent in milk. Its effect is striking in the extreme and becomes apparent two or three hours after seeding with the organism.

Since liver and kale, the richest known sources, have remarkable nutritive properties for higher animals, the latter being of extraordinary value for poultry and dairy cows, we suspect that the "growth substance" under consideration is of importance in the nutrition of animals as well as of the organism which we are using as a tool.

This nutrilite has a tendency to be associated with proteins, such as casein and egg albumin, to such an extent that for a considerable period of time we worked upon the supposition that the substance was an unknown amino-acid such as is being investigated by Rose[2] and his co-workers. It was later found, however, that careful purification of casein previous to hydrolysis removes all but traces of the stimulating substance.

Concentration of the "growth factor" has been accomplished to such an extent that one part of the preparation gives a response when added to ten million parts of culture medium. The preliminary steps in the concentration are the same as are used by Kuhn[3] in the preparation of lactoflavin. That our growth factor is not lactoflavin itself is shown by the fact that its physiological effect is practically unimpaired by long exposure to light, whereas under the conditions used the lactoflavin present in the preparation was largely decolorized and destroyed. Also through the kind courtesy of Dr. Kuhn, of the Kaiser-Wilhelm Institut in Heidelberg, we have been furnished a sample of pure crystalline lactoflavin which gives negative results when used as a substitute for our cruder material. We can not be sure, however, that pure lactoflavin is not *one* factor concerned in the response.

It appears that in the later steps of the purification of lactoflavin, material is discarded which is physiologically very active (at least toward certain lower organisms). This interpretation is in line with the recent work of Booher[4] who finds that what may be regarded as a crude lactoflavin preparation is effective for experimental rats, under conditions where Kuhn finds the pure pigment to fail entirely.

Our results would call in question the usefulness of such partially refined lactoflavin preparations as that of Itter, Orent and McCollum,[5] which may or may not owe its physiological action to lactoflavin itself. It should be noted that from 10 pounds of whey powder these workers recovered only what is equivalent to about 700 units of "vitamin G." This can not be more than a one or two per cent. yield on the basis of that present in the original whey powder. This fact in itself indicates that something of outstanding importance has been discarded during the purification.

The nutrilite with which we are concerned is very stable; it is only partially destroyed by long autoclaving at 20 pounds pressure in 3N (or even 5N) H_2SO_4 solution, or in 2N $Ba(OH)_2$ solution. The concentration of this substance is being continued; it seems likely that the microorganism affected may be a valuable tool in helping to clear up the confusion regarding the number and chemical characteristics of the water soluble vitamins which remain as yet unknown.

ROGER J. WILLIAMS
BERT E. CHRISTENSEN
STATE AGRICULTURAL COLLEGE
CORVALLIS, OREGON

[1] Williams and Saunders, *Biochem. Jour.*, 28: 1887, 1934.

[2] Rose, *Proc. Amer. Soc. Biol. Chem.*, 8: 63, 1934.

[3] Kuhn, Gyorgy and Wagner-Jauregg, *Ber. der Deuts. Chem. Gesell.*, 66B: 1037, 1933.

[4] Booher, *Jour. Biol. Chem.*, 107: 591, 1934.

[5] Itter, Orent and McCollum, *Jour. Biol. Chem.*, 108: 579, 1935.

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A METHOD OF PREPARING PARAFFIN SECTIONS OF BONE

THE following method, while having no claim to originality, has given such satisfactory results that it seems worth while to suggest it to others.

Pieces of bone as large as $2 \times 2\frac{1}{2}$ cm by 2 mm have been used with excellent results. Decalcification may be carried out before or after the piece for sectioning is selected. For decalcifying, the writer uses 5 per cent. or 10 per cent. nitric acid, followed by a 5 per cent. solution of sodium sulfate (24 hours) and running water (24 hours). After dehydration, specimens are cleared with equal parts of absolute alcohol and chloroform, two changes of chloroform, and are then passed through several changes of paraffin (melting point 47° to 49°), and are finally embedded in harder paraffin (56° to 58°). Beginning in the morning, specimens can be dehydrated during the day, left over night in chloroform and infiltrated in paraffin and embedded the following day. It is possible to embed small pieces of bone within 14 hours after removing them from 70 per cent. alcohol. For rapid embedding it is essential that the solutions and specimens are kept in tightly stoppered bottles and that the atmosphere is fairly dry; occasional gentle shaking hastens diffusion. Relatively large amounts of solutions are desirable, and these may be used repeatedly if kept well stoppered.

After embedding, the side of the bone to be sectioned is exposed to water,[1] and best results are obtained for most bony structures only when the entire surface to be sectioned is exposed. After remaining in water until the tissue shows a noticeable swelling, usually from 2 to 10 days, the exposed surface is dried and dipped in melted paraffin, which is then more uniformly mixed with the original paraffin block by means of a hot needle. If cutting becomes more difficult after a few sections are removed, the block should be returned to water for a longer period.

Serial sections (10 μ) are cut and mounted with water-glass fixative: 100 cc of water, 1 cc standard water-glass solution and 1 cc concentrated ammonia water.[2] (Treating of sections with 70 per cent. alcohol slightly acidified as recommended by Ullrich has been unnecessary for our work.) Clean slides are flooded with the solution, sections added, the whole warmed slightly and the excess fluid drained. Slides should be dried at least 48 hours. The use of water-glass fixative has eliminated one of the most serious difficulties previously encountered in making paraffin sections of bone; namely, the loss of sections in the staining process. This loss, of course, can be avoided by treating the slides with a thin solution of celloidin, but this is more trouble than the use of water-glass fixative. The fixative containing gum arabic and potassium bichromate mentioned by McClung[3] adheres bone sections perfectly, but interferes with staining.

Good results have been obtained both from solid bone of homogeneous structure (hyperostosis in chickens) and from bone containing regions of varying hardness and different structures (for example, entire tibia-fibula of chick embryos near hatching, single specimens containing both epiphysis and diaphysis of bones from adult chickens, and cervical vertebrae). Excellent longitudinal sections through three vertebrae and the included spinal cord have also been obtained; larger pieces have not been attempted.

Haemalum and eosin give good staining results following this technique.

LORNA THIGPEN DAVID
STORRS AGRICULTURAL EXPERIMENT STATION
STORRS, CONN.

[1] Elizabeth C. and Eugene Cutuly, SCIENCE, 80: 564–565, December 14, 1934.

[2] H. Ullrich, "Aufkleben von Paraffinschnitten mit ammoniakhaltiger Wasserglaslösung," Planta 10, 1930.

APPARATUS FOR HEAVY WATER STUDIES IN SMALL ANIMALS

WHEN heavy water is given to animals, it becomes important both to follow its content in the living organism as well as (for economic reasons) to recover the material after it has left the body.

These ends have both been served in the employment of simple modifications of the Haldane metabolism train, which we shall briefly describe. The apparatus shown in the figure was used in establishing the depressant effects of heavy water on the mammalian metabolism, as recently reported by one of us[1] to the Society for Experimental Biology and Medicine.

The mouse in chamber E receives a stream of air free from carbon dioxide and water. The CO_2 is removed as it passes through A and B, while concentrated sulfuric acid in C (bubbling flask) and D (pumice granules saturated with H_2SO_4) removes the water. The size of condenser A protects the train against the large amount of CO_2 given off by dry ice in close proximity.

[3] C. E. McClung, "Handbook of Microscopical Technique," p. 129. Paul B. Hoeber, Inc., New York, 1929.

[1] H. G. Barbour, *Proc. Soc. Exp. Biol. and Med.*, 32: 8, 1935.

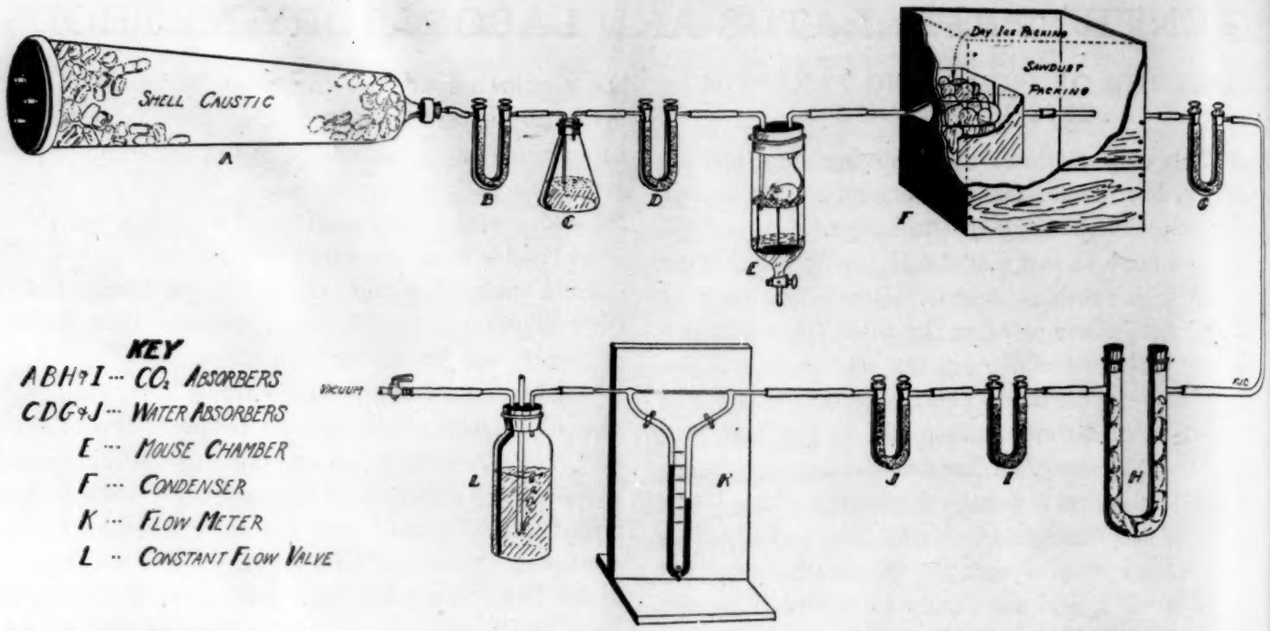

FIG. 1.

The mouse chamber itself contains mineral oil enough to cover the feces, which rest on the lower mesh platform. The urine falls to the neck of the chamber and can be drawn off by the stopcock, free of oil. A coarser mesh platform supports the mouse at a level high enough to prevent the tail touching the oil.

From the chamber the air passes into the condenser (F) consisting of an ordinary 100 cc pipette, the end of which is seen projecting from the box. The pipette is enclosed in dry ice well insulated with sawdust.

The "insensible perspiration," consisting of all the water vapor from the animal's lungs and skin, accumulates as snow in the pipette. Within one day the apparent size of the snow pile approaches that of the mouse itself. In a series of fifty-one determinations, it was found that 97.9 per cent. of the total water vapor was thus caught in the pipette, the sulfuric acid in G trapping the remainder.

Expired CO_2 is caught in absorbers H and I (shell caustic moistened by three and one drops of water, respectively). Absorber J (H_2SO_4 and pumice) is weighed together with H and I.

The air flow measured by the venturi meter (K) is kept at a constant rate of 200 cc per minute by means of the constant-flow water valve (L).

The specific gravity of the insensibly lost water or (if oil be omitted from the chamber) of the total water lost by the mouse is quickly determined from 0.01 cc of the melted snow by the falling drop method of Barbour and Hamilton.[2] The D_2O percentage of the mixture is calculated from the formula $\frac{G-1}{.1079}$, where G is the specific gravity. The denominator is the fractional part of the specific gravity of pure deuterium oxide (Urey and Teal[3]).

This simple calculation of the D_2O content from a linear specific gravity curve leads to an error in the D_2O volume of not over 0.05 per cent. (Lewis and Luten[4]).

Some idea of the value of the insensibly lost water as an index to the actual D_2O/H_2O ratio prevailing in the living body may be gained by the following comparisons in the two mice, from the carcasses of which about two thirds of the water was regained by distillation:

DEUTERIUM OXID (PER CENT. OF TOTAL WATER)

	Mouse No. 12	Mouse No. 10
Found in insensibly lost water last 12 hours before death	3.8	11.6
Found in carcass (redistilled from acid K_2MnO_4 by courtesy of Dr. Paul K. Smith)	3.6	10.1

HENRY G. BARBOUR
F. J. COCHRAN

YALE UNIVERSITY

[2] *Jour. Biol. Chem.*, 49: 625, 1926.

[3] *Rev. of Mod. Physics*, 7: 34, 1935.

[4] *Jour. Am. Chem. Soc.*, 55: 5061, 1933.

BOOKS RECEIVED

Bulletin of the National Research Council, No. 97. Pp. 51. National Academy of Sciences, Washington. $1.00.

DAVIS, H. T. and W. F. C. NELSON. *Elements of Statistics.* Pp. xi + 424. Principia Press.

JENNINGS, H. S. *Genetics.* Pp. xi + 373. 70 figures. Norton. $4.00.

KRONIG, R. DE L. *The Optical Basis of the Theory of Valency.* Pp. x + 237. 67 figures. Cambridge University Press, Macmillan. $4.50.